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Antifungal drugs

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ABSTRACT

Fungal infections continue to emerge as an important cause of infectious disease and mortality in humans. Amphotericin B deoxycholate (ABD), was the first antifungal that was discovered, and it was released in 1958, and flucytosine, which was developed later and is effective against *Candida* and *Cryptococcus*, was introduced in 1978. The discovery of first-generation azoles (fluconazole and itraconazole) in the 1990s has created a new step in the treatment of fungi. In the years that followed, with the development of lipid formulations of amphotericin B, the introduction of second-generation azoles, and the release of the most recently developed class, echinocandins, the foundations of today's existing antifungal classes were laid. This article is aimed to review the mechanism of action, side effects and clinical use indications of the main antifungal drugs used in the treatment of systemic fungal infections.

Keywords: Antifungal, mycology, fungal infection

THE HISTORY OF ANTI-FUNGAL DRUGS

Fungal infections continue to emerge as an important cause of infectious disease and mortality in humans.[1] In the present day, immunosuppression, which has emerged as a therapeutic side effect of life-saving treatments developed for the treatment of various malignancies and rheumatological diseases, predisposes patients to invasive fungal infections.[2]

Amphotericin B deoxycholate (ABD), was the first antifungal that was discovered, and it was released in 1958, and flucytosine, which was developed later and is effective against *Candida* and *Cryptococcus*, was introduced in 1978. However, in the case of ABD its nephrotoxicity, and the bone marrow suppression of flucytosine as well as the rapid development of resistance when used alone limited their use.[1]

The discovery of first-generation azoles (fluconazole and itraconazole) in the 1990s has created a new step in the treatment of fungi. In the years that followed, with the development of lipid formulations of amphotericin B, the introduction of second-generation azoles (voriconazole, posaconazole) in the 2000s, and the release of the most recently developed class, echinocandins, the foundations of today's existing antifungal classes were laid.[1,3,4] This article is aimed to review the mechanism of action, side effects and clinical use indications of the main antifungal drugs used in the treatment of systemic fungal infections.

ANTIFUNGAL DRUG CLASSES

There are three main classes of antifungal drugs that are used in the treatment of systemic fungal infections. These consist of; polyenes that bind to ergosterol in the fungal cell membrane (not found in the mammalian cell membrane) and impair the permeability of the membrane hence exerting fungicidal effects, azoles that disrupt ergosterol biosynthesis, and echinocandins, which are not found in mammalian cells, and prevent fungal cell wall formation by non-competitively inhibiting the synthesis of β-(1,3)-D-glucan, which is the main component of the fungal cell wall.[5]

1. Polyenes

Amphotericin B, which is a natural product of Streptomyces nodosus, is the only antifungal agent in the polyene class.6 The first formulation of amphotericin B was Amphotericin B deoxycholate, followed by 3 different lipid-related formulations (amphotericin B colloidal dispersion, amphotericin B lipid complex, liposomal amphotericin B) that were developed to reduce its nephrotoxic side effects.[7]

Activity spectrum: The majority of *Candida*, *Aspergillus*, *Mukorales* and *Cryptococcus* species are effective against dimorphic fungi, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *posadasii*, *ParaCoccidioides* spp.[7,9]

Resistance: It is often because of reductions in ergosterol synthesis and the synthesis of alternative sterols that prevent Amphotericin B from binding to the cell membrane. Amongst *Aspergillus terreus*, *Scedosporium* spp. and *Tricosporon* spp., and *Candida* species primary resistance is most common in *C. lucitaniae* and *C. auris*.[7]

Pharmacology: Amphotericin B deoxycholate (ABD), amphotericin B lipid complex (ABLC), and liposomal amphotericin B (LAMB) are formulations that are currently available. A different lipid-based formulation known as Amphotericin B colloidal dispersion, is being produced today.[1,7]

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Along with some tried local applications (such as bladder irrigation, intraperitoneal, intrathecal, inhaler, intravital), usually all formulations are administered parenterally.[7,10]

The pharmacokinetics vary between individual formulations of amphotericin B. ABD, is found to be highly bound to serum proteins (especially β-lipoprotein) and accumulates in various body tissues and fluids, which include the liver, spleen, pleural fluid, peritoneal fluid, joint, vitreous, and aqueous humour.[7,11] Elimination of amphotericin B is biphasic, with a terminal half-life of around 15 days. No metabolites of ABD have been identified. Most of the drug is broken down in situ, and a small part is excreted in the urine and bile.

The serum concentrations are not affected by hepatic or renal function, hemodialysis or peritoneal dialysis. Higher doses are required for lipid-based formulations to achieve the same therapeutic effect as with ABD.[1,7] Unlike other lipid formulations of liposomal amphotericin B, serum concentrations are not lower than those obtained with the same dose of ABD, and the amount of unbound amphotericin is less when compared to that for ABD.[7]

Dosing: The daily dose of ABD for most invasive mycoses is 0.5-1 mg/kg. For invasive *aspergillosis* and *mucormycosis*, a daily dose of 1-1.5 mg/kg is recommended until patients recover. Daily doses of 1.5 mg/kg should not be exceeded. The recommended daily dose for LAMB and ABLC is 3-6 mg/kg.[1,7]

Clinical indications: Amphotericin B is an antifungal agent that is effective in the treatment of many invasive fungal infections (such as *cryptococcosis*, *blastomycosis*, *mucormycosis*, *candidiasis*, *aspergillosis*, *sporotrichosis*). As a result of the nephrotoxicity effect especially due to the formulation of ABD, the use of safer antifungals such as echinocandins has been limited in some fungal treatments except for serious and life-threatening diseases. It is recommended as first-line treatment for *cryptococcal meningitis* and *mucormycosis*.[7,12]

Toxicity: Particularly, the most serious side effect of the ABD formulation is nephrotoxicity. Nephrotoxicity is thought to be a result of its vasoconstriction effect on renal afferent arterioles. Aside from this, side effects such as electrolyte disorders, transfusion reactions, thrombocytopenia, leukopenia, tinnitus may also be observed. The incidence of nephrototoxicity is lower in lipid formulations. An infusion reaction, which is thought to be related to type 1 hypersensitivity with symptoms such as chest pain, shortness of breath, hypoxia, abdominal pain, flushing and urticaria, can be seen after LAMB infusion, and it can be successfully managed with diphenhydramine treatment and short-term discontinuation of the drug.[7]

2. Azoles

Azoles are a class of drug that inhibit the enzyme lanosterol-14α-demethylase, which prevents the binding of ergosterol by altering the functionality and structure of the fungal cell membrane. Along with the discovery of azole class antifungals, a very important alternative has been found in the treatment of systemic fungal infections. Azole are divided into two groups as triazoles (fluconazole, voriconazole, itraconazole, posaconazole and isavuconazole), and imidazoles (ketoconazole, micanazol).[13]

Activity and resistance spectrums:

- **Fluconazole**: It has very effective activity against *Candida* species in general, but low activity against *C. glabrata* and no activity against *C. krusei*. It shows activity against *Histoplasmosis*, *Blastomyces*, *Coccidioides* and *Paracoccioides* spp., however not as much as itraconazole. It also has excellent activity against the *Cryptococcus* species. It shows no activity against *Aspergillus*, *Fusarium*, *Scedosporium* species and *Mucorales*.[7,14]
- **Voriconazole**: It is similar to fluconazole in terms of activity against *Candida*, but it also shows in vitro activity against fluconazole-resistant *C. glabrata* and *C. krusei*. It is resistant against dimorphic fungi such as *B. dermatitidis*, *H. capsulatum*, and *C. immitis*, and shows activity against most *Aspergillus* species including amphotericin B resistant *A. terreus*, *Fusarium* spp. and *Scedosporium* spp., however very low activity against *Mukorales* species.[15-17]
- **Itraconazole**: It demsontrates activity against Sporothrix schenckii and *Aspergillus* spp. species, as well as against dimorphic fungi such as *B. dermatitidis*, *H. capsulatum*, and *Coccioides* spp.[17]
- **Posaconazole**: It demonstartes activity against most *Candida* species, *Cryptococcus*, *B. dermatitidis*, *H. capsulatum*, *C. immitis*, *Aspergillus* species including *A. terreus*.[14] In addition, it shows activity against some *Mukorales* species.[14,15,17]
- **Isavuconazole**: It shows activity against most *Candida* species including *C. glabrata* and *C. krusei*, *Cryptococcus*, *B. dermatitidis*, *H. capsulatum*, *C. immitis*, as well as *Aspergillus* species including *A. terreus* species and the *Mukorales* group.[18]

Resistance: The lanosterol 14α-demethylase mutation in *Aspergillus*, *Cryptococcus* and *Candida* constitutes the basic mechanism of azole resistance. As a result of azole cross-resistance, most flucoazole-resistant organisms are also resistant against voriconazole. Another azole resistance mechanism is the eflux pump, which reduces the concentration of the drug in the cell.[19]

Pharmacology:

- **Fluconazole:** Fluconazole, is available in both tablet and intravenous (IV) formulations and has a very high oral bioavailability. In oral use, >90% of the drug can be found in the circulation and 80% is found unchanged in the urine. Its absorption is not affected by food and gastric pH. A small portion of it (10%-12%) is protein-bound and distributes very well into body fluids, including the CSF. Due to its long half-life, it can be administered once a day and a loading dose of 2 times the daily dose (100-400 mg/day) is recommended. In cases of renal failure, dose reduction is recommended.[20]
- **Voriconazole:** It is available in tablet, oral suspension and IV formulations. Its oral bioavailability is over 90% and decreases by about 30% with fatty foods. Vorconazole is extensively metabolized by CYP 450 enzymes in the liver, and toxicity or therapeutic failure may occur as a result of polymorphisms in these enzymes. Adult normal dosing: In oral formulations, 200 mg twice a day (which can be increased to 300 mg according to therapeutic drug monitoring), in IV formulation, the first 2 doses are 6 mg/kg 12 hours apart, then 4 mg/kg every 12 hours. Serious side effects such as hepatitis and delirium have been reported at doses that exceed 6 µg/mL daily.[21,22] Therapeutic drug monitoring is recommended to ensure efficacy and prevent toxicity. Body distribution including CSF is very good. It is not recommended for the treatment of urinary tract infections since it is excreted in the urine

in very small amounts. Due to the accumulation of the cyclodextrin component in the IV formulation in the kidney, IV use is not recommended in patients with CrCl <50 mL/min. For patients with mild to moderate chronic hepatic impairment (Child-Pugh Class A and B), it is recommended to reduce the maintenance dose by 50% following the full loading dose.[22]

- **Itraconazole:** While there are 2 formulations that widely available, being capsules and oral solution, an IV formulation is also used in some countries. In addition, a formulation called SUBA itraconazole (super bioavailability-itraconazole) was approved by the FDA in 2018 in order to increase bioavailability (173%).[23] The oral bioavailability of the capsule formulation is approximately 55% and this ratio increases along with food and acidic pH, whereas the oral bioavailability of the solution formulation is higher (about 30% more) and is unaffected by food and gastric pH. Gastric side effects are more commonly observed with the oral solution and some patients cannot tolerate this form of the drug.[24] Contrary to voriconazole and fluconazole, its concentration in CSF and eye fluid is very low, while accumulation is 20 times higher than the plasma concentration in the nails and skin. Itraconazole is extensively metabolized by liver CYP450 3A4, with one active (hydroxyitraconazole) and several inactive metabolites excreted in the urine and faces. As its active metabolite is not found in the urine, it is not recommended for the treatment of urinary tract infections. No dose adjustment is required in renal failure, but dose reduction is recommended in patients with hepatic impairment.[25]
- **Posaconazole:** Along with oral suspension, delayed-release tablet and intravenous form, there are three formulations available of this drug.[20] Although absorption increases with fatty foods in suspension formulation, the tablet formulation is not affected by food intake.[20,26] It is largely bound to plasma proteins (98%) and is metabolized by uridine diphosphate (UDP)-glucuronidation and excreted through the bile and faeces.[27] No dosage adjustment is necessary for the treatment of renal failure and liver disease. While it penetrates well in most body parts, it has a very low CSF penetration like in the case of itraconazole. Data on the treatment of CNS infections with this drug are limited. Its half-life is approximately 27 hours, so while once-daily administration is sufficient in IV and tablet formulations, more frequent dosing may be needed in suspension formulations as the absorption may be different.[20]
- **Isavuconazole:** It is available in two formulations, both oral capsule (100 mg) and intravenous formulation, and it does not contain cyclodextrin within its IV formulation. For isavuconazole, which has a very long half-life (approximately 130 hours), a single daily dose is sufficient following a 48-hour loading dose.[20] Its oral bioavailability is very high (98%) and is not affected by food and gastric Ph.[28] It is widely distributed into body tissues, however data on CNS infections is limited. Given its high bioavailability and consistent metabolism, inter-patient variability in drug levels is lower for isavuconazole when compared to posaconazole, itraconazole, and voriconazole. It is extensively metabolized by CYP 450 enzymes in the liver and excreted in the faces. The concentration in the urine is below 1% and does not require dose adjustment in renal failure.[20,28] Dose adjustment is also not recommended in Child-Pugh class A and B patients with liver disease.[20]

Clinical indication:

- **Fluconazole:** Fluconazole is an effective anti-fungal agent for oropharyngeal *candidiasis* (100-200 mg/day), esophageal *candidiasis* (200-400mg/day 14-21 days), symptomatic *Candida cystitis* (200 mg/day for 2 weeks), and vulvovaginal *candidiasis* (150 mg/day single dose). Although echinocandins are generally recommended as the first-line treatment in candidemia, fluconazole is a good alternative agent in patients that don't have critical illness and have no possibility of resistance to fluconazole.[20] It has been found to be effective in the consolidation treatment of *critococcal meningitis*, in patients with mild to moderate pulmonary *cryptococcosis*, in patients with *coccidioidomycosis* including meningitis, and in the prophylaxis of neutropenic patients against fungal infections. However, it is not effective against invasive molds and should not be used in patients with *aspergillosis*, *mucormycosis* and *scedosporiosis*.[20,29,30]
- **Voriconazole:** Voriconazole was licensed for use in the treatment of invasive *aspergillosis* following a multicenter study comparing it with amphotericin B in the treatment of *Aspergillus* (31). It has also been found effective in other invasive *aspergillosis* including CNS *aspergillosis* and non-invasive *aspergillosis* such as bronchopulmonary *aspergillosis*. It has been approved for the treatment of mucosal and invasive *candidiasis* but not recommended as first-line therapy. It has also been found to be effective in the treatment of *Scedosporium* spp. and *Fusarium* spp. It has been found to be effective in the treatment of *Cryptococcus* and endemic mycoses, however its use in these patients is limited to situations where other antifungals are not used.[20]
- **Itraconazole:** It has been found to be effective against several cutaneous and invasive fungal infections. It is approved for use in bronchopulmonary and invasive *aspergillosis*, *coccidioidomycosis* including meningeal infection (not recommended due to poor CNS penetration), *Histoplasmosis*, *sporotrichosis*, *blastomycosis* and *paracoccidioidomycosis*. It has been shown to be effective in oropharyngeal, esophageal and vaginal *candidiasis*, but it is not recommended as first-line therapy as it has not been shown to have a significant superiority compared to fluconazole. In the treatment of invasive *aspergillosis*, its use is recommended only in patients that develop intolerance to voriconazole and amphotericin B.[20,32,33]
- **Posaconazole:** According to studies performed, posaconazole was demonstrated to be more effective in preventing invasive fungal infections than fluconazole and itraconazole.[34] Its use has been approved for the prophylaxis of oropharyngeal *candidiasis* and invasive fungal infections.[20,35]
- **Isavuconazole:** In a study that compared voriconazole and isavuconazole for the treatment of invasive *aspergillosis* and other filamentous fungi, it was reported that isavuconazole was not behind voriconazole in terms of efficacy and survival, and its side-effect profile was lower than voriconazole.[36] In a different study, it was reported that it was effective against *mucormycosis* and had similar efficacy when compared to patients treated with amphotericin B.[37]

Toxicity: Triazoles are generally well tolerated, however gastrointestinal system (GIS) side effects such as nausea, abdominal pain, and vomiting may occur. Especially in itraconazole oral solution, GIS side effects are reported more often.[38] Hepatic dysfunction is a side effect that can be seen with all azoles. Mild transaminase elevation may cause more serious clinical manifestations such as cholestasis and fulminant liver failure. High-dose therapy, drug interactions and genetic polymorphisms that increase systemic exposure to azoles may increase the risk of hepatotoxicity.[20]

3. Echinocandins

Echinocandins are the most recently discovered class of antifungals, and there are three antifungal agents in this class: caspofungin, anidulafungin, and micafungin.

Mechanism of action: It disrupts the structure of the fungal cell wall by inhibiting (1→3)-β-d glucan synthase, which is required for the synthesis of (1→3)-β-d glucan, which participates in the structure of the cell wall.[39] Beta glucan constitutes approximately 30-60% of the cell wall mass in *Candida* species. Thus, a reduction of beta glucan causes a fungicide effect in *Candida* species.[40] In filamentous fungi such as *Aspergillus*, beta glucan is concentrated at the apical ends of the hyphae, and therefore echinocandins can cause fungistatic effects.[41]

Activity and resistance spectrums: Echinocandins act primarily on *Candida* and *Aspergillus* species, however, show little activity against other yeasts, including *Cryptococcus*, and moulds aside from *Aspergillus*.[39] While all three classes of echinocandins exhibit very good activity against most *Candida* species, including antifungal agents *C. albicans*, *C. glabrata* and *C. tropicalis*, high minimum inhibitory concentrations (MIC) are required for *C. parapsilosis* and *C. guilliermondii*.[39,42] They have no activity against *Cryptococcus* and *Trichosporon* species, endemic dimorphic fungi, *Mucorales*, *Scedosporium* and *Fusarium* spp.[15,39]

Pharmacology: Despite that echinocandins share similar spectrums of activity, each agent differs in the pathway of metabolism. They are minimally absorbed via oral administration; therefore, only intravenous formulations are available.[42] They are highly bound to plasma proteins, their penetration into urine, CSF, brain, prostate, and ocular fluid is weak as a result of their large molecular weight and high plasma protein binding.[39,43] Due to their long half-lives, they are administered as a single daily dose (caspofungin 70 mg after loading 50 mg/day maintenance, anidulafungin 200 mg after loading 100 mg/day maintenance, micafungin 100 mg/day single dose).[39] None of them are major substrates, inducers, or inhibitors of CYP450 enzymes and the P-glycopeptide transport system, hence showing fewer drug interactions. They are converted to inactivated metabolites through non-enzymatic means and are largely excreted via the faecal route.[44] Since the amount of the drug that is excreted in the urine is very minimal, they are not affected by dialysis and kidney failure, and dose adjustments should be made only for caspofungin in the case of liver failure.[39]

Clinical indication: For the treatment of candidemia and invasive *candidiasis*, echinocandins are a better treatment option than amphotericin B and azoles, as they have fewer side effects and higher survival rates. In the guidelines, echinocandins are recommended as the first-choice agent in patients with candidemia.[45] Its use may be more limited in *Candida* infections such as meningitis, endophthalmitis, and urosepsis as a result of tissue-related pharmacokinetic reasons. It is the most effective antifungal class in the treatment of amipiric fungal infection in febrile neutropenic patients. Especially caspofungin has been approved for use in this patient population.[39] In the treatment of *Aspergillus*, it is not recommended in first-line therapy, however it can be used as rescue therapy in patients who do not respond or cannot tolerate other agents.[46]

Toxicit: Echinocandins are well tolerated, and all three members of the class have similar side effects. Serious side effects that require discontinuation of the drug are less common when compared with other systemic antifungal classes. Slight increases in liver enzymes, rarely infusion and hypersensitivity reactions, gastrointestinal side effects such as pain at the injection site, nausea, vomiting, diarrhea, and abdominal pain can be observed. Rarely, cardiac and hematopetic side effects have also been reported.[39]

4. Flucytosine

Flucytosine is an analogue of pyrimidine, which is taken into the fungal cell through the cytosine permease enzyme and converted to fluorouracil by the cytosine deaminase enzyme, it inhibits nucleic acid synthesis and hence protein synthesis.[47]

Activity and resistance spectrums: The majority of its activity spectrum is limited to yeasts and shows activity against most *Candida* species. It has no activity against dimorphic fungi and filamentous fungi. Resistance to flucytosine may appear intrinsically or can be acquired. Intrinsic resistance is seen due to mutation in cytosine permease, and acquired resistance is usually observed due to mutations in cytosine deaminase and uracil phosphoribosyl transferase enzymes.[47,48]

Pharmacology: Due to its high bioavailability, flucytosine can be used orally. It is only available in an oral formulation in the United States, whereas an intravenous formulation is also available in Europe. It is absorbed by approximately 80-90% following oral administration. It is widely distributed throughout the body and has a low binding to plasma proteins. Concentrations of flucytosine in the spleen, heart, liver, kidney, and lung are equal to serum concentrations. CSF concentrations are approximately 60-80% of serum concentrations, while urine concentrations are several times higher than serum concentrations. Its half-life is 6 hours on average and 96% of the total dose is excreted unchanged within the urine.[48]

Clinical indication: For the treatment of *cryptococcal meningitis* induction, it is the used alongside amphotericin B as the first line of treatment. In countries where amphotericin B is not available, it is also used in combination with fluconazole. Due to the rapid development of resistance, its use as monotherapy is not recommended. As a result of high urine concentrations, it can only be used as monotherapy in *Candida cystitis*.[49]

Toxicity: The most significant are, hematological, hepatic and GIS sides effects. Especially the development of thrombocytopenia and leukopenia may limit the use of the drug. GI side effects such as nausea, vomiting, and diarrhoea can be observed in 6% of patients.[47]

CONCLUSION

- There are three main classes of antifungal drugs that are used in the treatment of systemic fungal infections: polyenes, azoles and echinocandins.
- Amphotericin B is recommended as first-line treatment for *cryptococcal meningitis* and *mucormycosis*.
- Along with the discovery of azole class antifungals, a very important alternative has been found in the treatment of systemic fungal infections.
- Echinocandins act primarily on *Candida* and *Aspergillus* species, however, show little activity against other yeasts, including *Cryptococcus*, and moulds aside from *Aspergillus*.

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